Remarks

Claims 84, 85, 89-93 and 95-104 are pending following entry of the claim amendments herein. Claims 84 and 95 have been amended, and Claims 103 and 104 have been added. The marked up copy of the amendments to the claims is attached hereto and is captioned "Version with Markings to Show Changes Made."

New Claims 103 and 104 are similar to Claims 84 and 95, respectively, except that new Claims 103 and 104 specifically recite that the native cancer antigen is the "Her2/*neu* gene product". These claims are supported by the specification as filed, *e.g.*, at page 17, lines 31-34.

Applicants note with appreciation that the art rejections raised in the previous Office Action have been withdrawn. The claims stand rejected under 35 U.S.C. § 112, first and second paragraphs for lack of enablement and indefiniteness. These rejections will be addressed below.

I. **Rejections under 35 U.S.C. § 112, second paragraph.**

Claims 84, 85, 90-83 and 95-102 stand rejected under 35 U.S.C. § 112, second paragraph on various grounds of indefiniteness. The individual indefiniteness rejections will be discussed below.

"Immunogenically Effective Amount."

The Office Action states that the claim term "immunogenically effective amount" is unclear in that "it is unclear whether 'an immunogenically effective amount' is that amount required to elicit any amount of immunogenic response to the antigen expressed by the alphavirus particle or whether 'an immunogenically effective amount' is that amount required for eliciting an immunogenic response of sufficient magnitude to elicit a therapeutic effect to treat a cancer cell." (Office Action, page 3, second paragraph).

Applicants have amended independent Claims 84 and 95 herein to recite that the composition is provided in an "immunogenically effective

amount to prevent or treat cancer." This amendment is supported by the application at page 7, lines 2-15, which states that the invention may be used to produce beneficial effects in the prevention or treatment of cancer.

Accordingly, Applicants submit that the claims as amended clearly define the metes and bounds of the claim and respectfully request that the outstanding indefiniteness rejection be withdrawn.

Native Cancer Cell Antigen.

The Office Action further states that the term "native cancer cell antigen" is unclear, stating that there are several descriptions thereof in the specification. Applicants' response is that the term "native cancer cell antigen" is intended to encompass any "naturally-occurring" cancer antigen as stated at page 7, line 6 and page 17, line 31. When viewed in context, the cited portion of the specification at page 9, line 32, is describing an embodiment of the invention in which cancer cells expressing an artificial antigen are administered to a cancer subject to induce an immune response against the subject's cancer (more fully described at page 9, lines 4-32). In one embodiment, cancer cells are removed from the subject and manipulated *ex vivo* to express the artificial cancer antigen. In an alternate embodiment, described in the section cited by the Examiner, cancer cells from another subject or source are manipulated to express the artificial cancer antigen. However, according to this embodiment, the exogenous cancer cells will typically need to share an antigen with the cancer subject's cells in order to effectively induce an immune response thereto. This discussion does not modify the definition of a "native cancer cell antigen"; it simply describes certain factors to be considered in using an artificial antigen according to a particular embodiment of the invention (*e.g.*, the exogenous cancer cells and the recipient's cancer cells will generally share an antigenic determinant so that immunity can be induced against the recipient's cancer cells).

Accordingly, Applicants respectfully submit that the meaning of the term "native cancer cell antigen" is sufficiently clear from the specification, as

"any naturally occurring cancer antigen", and respectfully request that the outstanding indefiniteness rejection on this basis be withdrawn.

"T-Cell Epitope and B-Cell Epitope."

Claims 91 and 100 stand rejected for indefiniteness on the basis that they recite T-cell epitopes and B-cell epitopes. The Office Action states that "the specification teaches immunogenic epitopes as T-cell and B-cell epitopes, it fails to disclose the metes and bounds of such epitopes." (Office Action, page 4, paragraph 2).

Applicants respectfully note that B-cell and T-cell epitopes are art-recognized terms and would be understood by those skilled in the art. Although it is not possible to provide an exhaustive list of all possible B-cell and T-cell epitopes, the terms would be clear to those skilled in the art.

To illustrate this point, Applicants are enclosing herewith an exemplary sample of materials printed from the internet that relate to B-cell or T-cell epitopes. It is apparent from the publications that B- and T-cell epitope mapping as well as methods of designing such epitopes are known in the art.

The enclosed course handout from the Microbiology 200 course at the University of Illinois at Urbana-Champaign defines B cell and T cell epitopes as follows:

> The B cell epitope is recognized by the antibody. It is often a surface exposed region of the antigen, i.e., the O-antigen of the lipopolysaccharide other (sic) gram-negative bacteria, such as Salmonella. The T-cell epitope is a peptide, which is presented in the context of the MHC molecule. It can be a portion of the molecule that is normally buried within the antigen. An example is a peptide from the flagellum of Salmonella.

In view of the foregoing, Applicants submit that the terms "B-cell" epitope and "T-cell epitope" are well-understood by those in the art. Accordingly, Applicants respectfully request that the outstanding indefiniteness rejection on this basis be withdrawn.

II. The Claims are Enabled.

Claims 84, 85, 90-93 and 95-102 stand rejected under 35 U.S.C. § 112, first paragraph as non-enabled, the Office Action stating that the specification does not enable those skilled in the relevant art to make and/or use the claimed invention. Specifically, the Examiner states that "Applicant's claims encompass the experimental and unpredictable field of *in vivo* cancer therapy in humans and other mammals" (Office Action, page 5, third paragraph), citing articles by Jain, Osband et al., and Gura. This rejection is respectfully traversed below.

The Jain article (Cancer and Metastasis Reviews 9:253-266, 1990) is relatively old, considering the revolution in the field of immunology over the past decade, and certainly does not represent the state of the art at the time of filing of the present application. Thus, this reference cannot provide definitive evidence required to sustain the present enablement rejection.

The Jain reference indicates that specific agents, such as antibodies, are preferred for the treatment of tumors (*see, e.g.*, paragraph spanning pages 261-62), because of their specificity for the target cells. The teachings of the cited Jain reference indicate that antibodies are good candidates as tumor therapeutics (Jain, page 261 right column to page 263 end of left column) because "[t]heir strengths include their high degree of specificity for tumor-associated antigens and the fact that exchange vessels and interstitium of tumors are more 'leaky' to macromolecules than those of several normal tissues" (Jain, page 261, right column, last paragraph). As stated in the Office Action, Jain goes on to teach "that the efficacy of cancer therapeutics, and therapeutic antibodies in particular, has been limited by the inability of the antibodies to reach target tumor sites *in vivo* in adequate quantities to elicit a therapeutic effect (see the abstract)." (Office Action, page 5, final paragraph). Nonetheless, Jain proposes a number of solutions to the perceived problem in 1990 of barriers to delivery of therapeutic agents to solid tumors (pages 261-64).

In fact, there are now at least two known examples of cancer/tumor antigen antibodies that have shown efficacy in humans. Herceptin® and IMC-225 are monoclonal antibodies that are on the market and in late-stage clinical trials, respectively. These treatments represent a passive immunity—rather than ask the patient's immune system to respond, Herceptin® and IMC-225 *are* the immune response—they substitute for the patient's immune system.

Herceptin® is a monoclonal antibody directed to the Her2/*neu* protein which is overexpressed in certain breast tumors. Herceptin® has shown positive therapeutic effects in women, alone or in conjunction with other therapies (*see, e.g.*, Hortobagyi, (2001) *Semin Oncol* **28**(6 Suppl 18):43-7; abstract enclosed). In clinical trials, Herceptin® has been demonstrated to be efficacious in certain human patients with advanced breast cancers, and is now being evaluated in women with earlier stages of the disease. IMC-225, or Erbituxan, is a monoclonal antibody directed against a receptor (the epidermal growth factor receptor, or "EGFR") found on many different types of cancer cells. IMC-225 is showing efficacy in human patients (Kim et al., 2001 Curr Opin Oncol 13:506; abstract enclosed); it was initially tested in mice bearing xenografts of human breast and vulval tumors (Fan et al., 1993 Cancer Res 53: 4322-8; Baselga et al 1993, J. Natl. Cancer Inst 85:1327; abstracts enclosed). The efficacy of these monoclonal antibodies in human patients establishes that the potential shortcoming posited by Jain et al. has been overcome, i.e. the administered antibodies ***can*** find the tumor cells. The potential remaining shortcomings for the use of passive immunity are that it can raise an immune response to the antibody itself, and it provides only one antibody, and in the case of monoclonal antibodies such as these two clinically-tested drugs, it addresses only a single epitope. Applicant's invention differs from these two drugs by employing active immunity. That is, by providing an immunogen or fragment thereof, the alphavirus-vectored immunogen will deliver the entire immunogen or immunogenic fragment, with the potential of multiple epitopes, to the immune system. Applicant

overcomes the potential shortcoming in terms of delivery by using an alphavirus that can target the immune system and deliver sufficient immunogen to mount a therapeutic effect.

The present inventors have demonstrated that the claimed compositions may be administered to achieve therapeutic effects *in vivo* in a mouse model of human breast cancer. These models, which have been very predictive of the efficacy of passive immunity approaches, should be equally predictive of the efficacy of active immunity approaches. The Declaration of Robert M. Olmsted Ph.D. pursuant to 37 C.F.R. § 1.132 (*hereinafter*, "Olmsted Declaration"), originally filed on July 26, 2001, presents data demonstrating that alphavirus replicon vectors expressing the HER2/*neu* oncogene provide protective effects against the development of mammary tumors in mice. Accordingly, in view of the state of the art and the data in the Olmsted Declaration, there is no objective reason to believe that the presently claimed compositions would be unable to achieve therapeutic effects in other mammals, including humans.

As a further shortcoming of the Jain publication, this reference is only focused on treatment of established tumors. The claimed compositions may also be used to prevent tumor initiation, establishment and metastasis. The comments of Jain regarding the "physiological barriers" of solid tumors to chemotherapeutic agents are not relevant to these other uses of the alphavirus vectors of the invention. In fact, Jain acknowledges the same in this article stating these barriers are not present in a number of tumor types citing the specific examples of cancers of hematologic origin (e.g. leukemias and lymphomas), (page 254).

Applicants' invention also addresses the potential shortcoming cited by Jain in terms of the difficulty in administering antibodies so that they are delivered efficiently to the tumors, since it is not necessary for the claimed alphavirus particles to enter the tumor or tumor cells at all. While not wishing to be limited by any theory of the invention, the alphavirus vector targets the immune system, not the tumor itself. The alphavirus vector infects antigen-

presenting cells, which results in a humoral and/or cellular immune response. The antigen-presenting cells will induce the activation of CD4 helper T-cells and the production of antibodies against the native cancer cell antigen expressed by the alphavirus vector. It is these antibodies and T-cells that will interact with the tumor cells to prevent tumor initiation, metastasis and/or induce tumor regression.

Additionally, the activation of CD4 helper T-cells provide the helper stimulus for the elicitation of CD8 cytotoxic T-cells (CTL). It is widely accepted in the art that cytotoxic T-cells are responsible for multiple examples of anti-tumorigenic effects demonstrated in both animal models. In addition, direct evidence of human clinical efficacy has been provided in patients treated with clonal populations of tumor-specific T-cells in adoptive therapy treatments (*see, e.g.*, Yee et al., 1997 Curr Opin Immunol 9:702). The Applicants' invention demonstrates the ability of the inventive methods to stimulate an active component of the cellular immune response. Indeed, Figures 4 and 5 of the present application describe the anti-tumor cellular immune response to HA in alphavirus vector vaccinated animals, and furthermore establish these cells are primarily responsible for the protection from tumor challenge in this model. The level of protection provided by the cellular component was not as stringent as that observed in mice vaccinated with the alphaviral vector with a fully intact immune response (*i.e.*, which would induce a cellular and humoral response), suggesting that both arms of the immune response were involved in providing the anti-tumor effects of the present invention. While not wishing to be limited by any theory of the invention, the ability to stimulate both arms of the anti-tumor immune response is believed t be desirable for achieving anti-tumor effects.

Thus, contrary to the assertion in the Office Action (page 6, lines 4-7), in view of (1) the data in the Olmsted Declaration demonstrating therapeutic effects with the claimed compositions in an animal model, and (2) the known animal and human efficacy of antibody therapies (i.e. passive immunity) in the art (*e.g.*, Herceptin® and IMC-225), and known animal and human efficacy of

CTL therapies (i.e. passive immunity) in the art, "conventional wisdom" would indicate that antibodies and/or CTL generated in the patient in response to administration of the claimed alphavirus compositions (i.e. active immunity) would also have therapeutic effects.

As a second point, the Office Action states:

> The specification teaches reduction of xenografted tumors in a mouse model. However, the art teaches that the mouse xenograft model is an inadequate model for predicting *in vivo* therapeutic efficacy for cancer. Osband et al. (Immunology Today, 11/6:193-195) teach that many immunotherapeutic agents are inactive in other species and that owing to the extreme complexity of the host-tumor immunorelationship, animal models do not fully mimic the biology of human patients with cancer (see especially the paragraph bridging pages 193-194). Gura (Science 278:1041-1042, 1997) teaches that xenograft tumors in mice don't behave like naturally occurring tumors in humans and that therapeutics which appear to be effective in the xenograft model often work poorly in humans (see page 1041, the entire document and especially column 2, last full paragraph).

Office Action, paragraph spanning pages 6-7.

Similar to the cited Jain publication, one shortcoming of Osband et al. is that it was published in 1990 and cannot reasonably be construed as representing the state of the art as of the filing date of the present application. Both Osband et al. and the 1998 Gura reference are focused on the shortcomings of current *in vitro* screening methods for potential small-molecule anti-cancer drugs (e.g. the NCI cell culture panels, referenced in Gura, which look for chemical compounds that "kill or inhibit" the cells, would not be useful for screening antibodies that react with such cells), and specifically the shortcoming of the xenograft model for assessing these types of anti-cancer drugs. These shortcomings are based on the inevitable species differences in uptake and metabolism of such small molecule drugs. In contrast, Applicant is not describing an anti-cancer drug and is not using a

xenograft model to assess a small molecule drug. In contrast, Applicant is claiming compositions that represent an immunological approach to preventing and/or treating cancer, which is fundamentally different than novel anti-cancer drugs which directly target the cancer, rather than the patient's immune system.

In the area of cancer immunotherapy, animal models are well-established for assessing the immunological potential of various treatments, and the two compounds discussed previously, Herceptin and IMC-225, which have shown efficacy in treating cancer in humans, were initially identified on the basis of animal trial efficacy. Both homologous ("syngeneic") and xenograft models have proven predictive (for xenograft models, see Modjtahedi et al 1993, Br. J. Cancer 67:254-61 (abstract enclosed), in which Mabs against a human gene that is over expressed in human tumors provided protection against tumor-forming xenografts of these human cells in mice; and Goldstein et al 1995 Clinical Cancer Res 1:1311-8 (abstract enclosed), in which the same tumor xenograft model in mice was used to show efficacy of IMC-225). Applicant has used a cancer animal model in which murine tumor cells are injected into mice. These murine tumor cells are first engineered to express the rat Her2/neu gene. As described by Nelson (WO 98/06863; copy enclosed), the murine breast cancer model has been predictive of immunological responses in breast cancer patients (page 3, lines13-26), as evidenced by Apostolopoulos et al. (Cancer Res 1994 54: 5186-93; abstract enclosed) and Peoples et al. (1995, Proc. Natl. Acad Sci. USA 92:432-436). The Nelson citation concludes with the statement that the cited clinical research "in addition to the association of improved survival with inflammatory infiltration of primary breast tumors, suggests that patients can mount an immune response to the malignant cells of breast tumors". The value of murine tumor models (syngeneic models) in which murine tumor cells can be engineered to express a tumor associated antigen, is further demonstrated by more recent papers utilizing and refining such models (e.g. Fenton RG et al 1995 J. Natl Cancer Inst 87:1853-1861; Penichet et al 1999 Lab Anim Sci

49:179-88; Sacco et al., 1998 Breast Cancer Res Treat 47:171; abstracts enclosed). Thus, the art indicates that studying immune responses of animals is predictive of immune responses in humans.

As noted in the Office Action, the working examples in the application describe immunization against an artificial cancer antigen to prevent tumor development and/or to induce tumor regression in a tumor expressing that "artificial" antigen. In these examples, the tumors are induced by administering engineered murine tumor cells (*see, e.g.*, Example 3; administration of LINE1 mouse lung carcinoma cells) to mice, not by xenografting a human tumor into an animal. The results in the Olmsted Declaration are based on a similar model that uses mouse tumor cells which have been engineered to express the rat *neu* oncogene. The use of the rat *neu* oncogene engineered into tumorigenic cell lines is a commonly used model for studying treatments for breast cancer (e.g. Esserman et al. 1999, Cancer Immunol Immunother 47:337-42; Brandt et al. 2001, Oncogene 20:5459-65, Robinson A 1995, CMAJ 153:1123-4; abstracts enclosed).

The Office Action appears to be applying Osband et al. for the proposition that "animal models do not fully mimic the biology of human patients with cancer" (sentence spanning pages 6-7). The Applicants respectfully submit that one currently skilled in the art, referencing the articles cited herein, would find the experiments described in the Olmsted Declaration as correlative with respect to other subjects, including humans. As discussed above, animal models based on tumor formation following administration of tumorigenic cells (whether of human or murine origin, whether transgenic for a tumor associated antigen or spontaneously tumorigenic) are art-recognized models of cancer. This recognition and acceptance of such models in the art creates a presumption that studies with these animals are correlative with cancer states in other subjects (*see* MPEP § 2154.02, "Correlation: *In Vitro/In Vivo*"). "In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating

unless the examiner has evidence that the model does not correlate" (*Id.*, emphasis added; *see also, In re Brana*, 51 F.3d 1560, 1566).

Moreover, the initial burden is on the Patent Office to set forth affirmative evidence that the "particular animal model" is not correlative with the claimed invention (*Id.*). With respect to the present application, the Patent Office bears the burden of presenting specific evidence as to why the particular animal model is not correlative of other subjects with cancer/tumors. This standard has not been satisfied by the outstanding enablement rejection. The citation of an out-dated general commentary by Osband et al. on the possible shortcomings of animal models has little probative value with respect to patentability of the present claims. Osband et al. set forth some caveats that must be considered when extrapolating animal data to humans; there will never be absolute certainty that results achieved in one animal model will apply to another. Such a high degree of certainty is not required ("A rigorous or an invariable exact correlation is not required"; *Cross v. Izuka*, 753 F.2d 140, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)). Animal models are clearly valuable "stepping stones" in identifying those compositions and therapies that will be effective for veterinary and medical purposes. As demonstrated by the numerous references cited herein, animal models are still widely used by those skilled in the field of cancer biology. These models have not been discarded or supplanted and, indeed, it is unlikely that they ever can or will be.

MPEP § 2164.02 sets forth a presumption that art-recognized animal models are enabling, unless the Examiner provides specific evidence to the contrary with respect to the particular animal model. This burden of proof is not satisfied by speculative statements regarding animal models in general. The "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (MPEP §2164.01). The Olmsted Declaration has demonstrated effective treatment of cancer in an established mouse model of mammary tumors. The clinical success of antibody therapies (*e.g.*, Herceptin® and IMC-225) supports the reasonable likelihood that the claimed approach will have therapeutic effects in human

subjects.

The Office Action points out that the working examples in the application do not describe administration of an alphavirus vector expressing a native cancer antigen. Applicants respectfully note that the presence or absence of working examples in the application is not dispositive of the enablement inquiry (*see*, MPEP §2164.02; *Gould v. Quigg*, 822 F.2d 1074, 1078; 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)). The specification describes alphavirus vectors (*e.g.*, Section E, pages 18-21), and the administration of alphavirus vectors expressing a native cancer antigen for the treatment of cancer (*e.g.*, Section D, pages 17-18). Methods of administering virus formulations are described in the application (*see, e.g.*, Section B, pages 14-15) and, in any event, are well-known in the art. The Olmsted Declaration describes administration of alphavirus replicon particles expressing a native cancer antigen (Her2/*neu*) using techniques of construction and administration described in the specification to achieve therapeutic effects in an animal model of human breast cancer.

In sum, Applicants respectfully submit that the description provides adequate guidance regarding the use of the presently claimed compositions as confirmed by the studies provided in the Olmsted Declaration. Applicants further submit that the statements in Osband et al. have been superceded by extensive results in the clinic based on animal trials and those in Gura regarding animal xenograft tumor models are not germane to the studies described in the Olmsted Declaration or the working examples, which employ an immunological approach not discussed by Gura.

In view of the foregoing, Applicants submit that the presently claimed compositions are enabled for use in treating cancer, *e.g.*, by preventing tumor initiation and/or spread and/or by inducing tumor regression. Accordingly, Applicants respectfully request that the outstanding rejection under § 112, first paragraph be withdrawn.

Conclusions.

The points and concerns raised by the Examiner in the outstanding Office Action having been addressed in full, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested. Should the Examiner have any remaining concerns, it is respectfully requested that the Examiner contact the undersigned to expedite the prosecution of this application to allowance.

Respectfully submitted,

Karen A. Magri
Registration No. 41,965

Customer Number:

20792
PATENT TRADEMARK OFFICE

Enclosures: Hortobagyi abstract
Fan et al. abstract
Baselga et al. abstract
Kim et al. abstract
Modjtahedi et al. abstract
Goldstein et al. abstract
Fenton et al. abstract
Penichet et al. abstract
Sacco et al. abstract
Esserman et al. abstract
Brandt et al. abstract
Robinson abstract
Apostolopoulos et al. abstract
Yee et al.
Peoples et al.
WO 98/06863
Internet publications on
B-cell and T-cell epitopes

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on March 26, 2002.

Sloan Hobbs

Version with Markings to Show Changes Made

84. (Three Times Amended) A composition comprising infectious alphavirus particles in an immunogenically effective amount to prevent or treat cancer, wherein said alphavirus particles comprise one or more heterologous nucleotide sequences encoding an antigen; and wherein said antigen is a native cancer cell antigen, and further wherein said alphavirus particles comprise one or more attenuating mutations.

95. (Twice Amended) A composition comprising infectious Venezuelan Equine Encephalitis (VEE) particles in an immunogenically effective amount to prevent or treat cancer, wherein said VEE particles comprise one or more heterologous nucleotide sequences encoding an antigen; and wherein said antigen is a native cancer cell antigen, and further wherein said VEE particles comprise one or more attenuating mutations.

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